REMARKS

Applicants thank Examiner Huynh for the courtesy of a telephonic interview on June 15, 2005, with the undersigned attorney and Duncan A. Greenhalgh. The independent claims were discussed in view of the art as well as the evidence of synergy. To clarify the statements made in the Interview Summary, Applicants understand that it was agreed with the Examiner to consider amending the claims, but it was not agreed that a claim amendment would be provided. In view of the Declaration of Joan W. Miller, M.D., attached hereto, Applicants respectfully submit that no amendment is needed and that the claims are patentable as they are currently pending.

Information Disclosure Statement

Applicants understand that the copy of reference C115, submitted to the Patent Office on April 18, 2003, is currently unavailable to the Examiner. Accordingly, Applicants provide a courtesy copy of this reference herewith.

Additionally, the Examiner has indicated that references C133, C134, and C138 have not been considered because no date was provided. Applicants understand that the dates of these references are all May, 2002. As a courtesy, a supplemental form PTO-1449 is provided herewith for the Examiner to initial to indicate consideration of these references.

Rejection Under 35 U.S.C. §103(a)

Claims 33-35, 39-43, and 47-49 are rejected under 35 U.S.C. §103(a), as unpatentable over U.S. Patent No. 6,270,749 to Blumenkranz *et al.* ("Blumenkranz") in view of Adamis *et al.* (1996), Arch. Ophthalmol. 114:66-71 ("Adamis") or U.S. Patent No. 6,342,219 to Thorpe *et al.* ("Thorpe"); claims 33-35, 39-43, and 47-49 are rejected under 35 U.S.C. §103(a), as unpatentable over Kramer *et al.* (1996), Ophthalmology 103(3):427-438 ("Kramer") in view of U.S. Patent No. 5,733,876 to O'Reilly *et al.* and Adamis or Thorpe; and claims 33-35, 39-43, and 47-49 are rejected under 35 U.S.C. §103(a), as unpatentable over Kramer in view of Blumenkranz and Adamis or Thorpe. Applicants submit that any of these combined teachings fail to teach or suggest a method where occlusion caused by administering an anti-angiogenesis factor, i.e., step (a), is synergistic with the occlusion caused by photodynamic therapy, i.e., steps (b) and (c), as required by claim 33. Similarly, Applicants submit that their combined teaching

fail to teach or suggest a method where the damage to the endothelial cells resulting from the combination of photodynamic therapy and administration of and anti-angiogenesis factor (i.e., steps (a), (b), and (c)) is greater than that resulting only from the sum of steps (a), (b) and (c), as required by claim 41. Moreover, such synergy is unexpected.

As provided in the Declaration of Dr. Joan W. Miller, Chair of the Department of Ophthalmology at Harvard Medical School and Chief of Ophthalmology at the Massachusetts Eye and Ear Infirmary, the synergistic effect on cell death when combining an anti-angiogenesis factor, such as angiostatin, with photodynamic therapy ("PDT") using a tetrapyrrole derivative, such as PDT using lutetium texaphyrin ("Lu-Tex") photosensitizer, a tetrapyrrole derivative, was unexpected, and was particularly unexpected in that it was seen primarily in endothelial cells and not in epithelial cells. (Declaration, paragraph 11.) The *in vitro* data provided in Table 1 of Example 1 of the patent application indicate that the interactive *in vitro* anti-endothelial effect of combined treatment with angiostatin and PDT using Lu-Tex photosensitizer are greater than additive when compared with the sum of expected effects of each treatment alone. (Declaration, paragraph 6.) In contrast, no effect was seen in an epithelial cell line, retinal pigment epithelium ("RPE") cells. (Declaration, paragraph 7.) Thus, synergistic cell death was seen in endothelial cells but not in epithelial cells in an *in vitro* system.

Applicants believe that these results are significant because, as described in the Declaration, occlusion of the vasculature is a major mechanism of PDT. Occlusion occurs by damage to the endothelial cells, with subsequent platelet adhesion, degranulation, and thrombus formation. (Declaration, paragraph 9 and Specification, page 14, lines 1-4.) However, repeated PDT treatments lead to cumulative damage to the RPE cells and choriocapillaris. This may lead to progressive treatment-related vision loss. (Declaration, paragraph 10 and Specification, page 3, lines 10-12.) These results support the potential of combining an anti-angiogenesis factor, such as angiostatin, with PDT, such as PDT using Lu-Tex photosensitizer, to improve eradication of chroidal neovasculature and to decrease deleterious effects on the RPE cells. (Declaration, paragraph 12 and Specification, page 26, lines 9-10.) Moreover, not only the synergy, but also the cell-specific selective synergy could not be predicted. (Declaration, paragraph 11.)

These *in vitro* results are borne out in an *in vivo* system as described in data presented in an abstract presented in May of 2003 at the Annual Meeting of the Association of Research in Vision and Ophthalmology in Fort Lauderdale, Florida (the "Abstract") (made of record as citation C115). For example, when PDT is conducted alone, using verteporfin photosensitizer and an irradiation dose condition of 10 J/cm^2, a lack of angiographic leakage was seen (i.e., CNV closure) 42.9% of the time at 24 hours and 7 days post-PDT. However, PDT under then same conditions in combination with continuous administration of angiostatin initiated before PDT (Declaration, paragraph 13) led to lack of angiographic leakage 90% of the time at 24 hours and 100% of the time at 7 days post-PDT. (Declaration, paragraph 13 and C115.) Given that administration of angiostatin alone had no effect (Declaration, paragraph 13), Applicants believe that the effect of PDT in combination with angiostatin is more than the additive result of treatment with angiostatin alone and with PDT alone. This confirms the synergy seen in the *in vitro* system.

In view of the Declaration provided by Dr. Miller, Applicants believe that the invention defined by independent claims 33 and 41 would not be obvious to the skilled artisan after reviewing the references applied in the Office Action. Claims 34-35, 39, 40, 42, 43, and 47-49, which depend directly or indirectly from an allowable base claim, also are allowable. Applicants respectfully request that this rejections be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants respectfully request that the foregoing rejections be reconsidered and withdrawn. The Examiner is invited to contact the undersigned attorney with any questions about this submission. Early favorable action is respectfully solicited.

Respectfully submitted,

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